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(54) Title: ALKYL-SUBSTITUTED CELLULOSE-BASED SUSTAINED-RELEASE ORAL DRUG DOSAGE FORMS (57) Abstract <p>Sustained release oral drug dosage forms that comprise a tablet or capsule of a plurality of particles of a solid-state drug dispersed in alkyl cellulose such as hydroxyethylcellulose or hydroxypropylcellulose. Once ingested the tablet or capsule disintegrates to disperse the particles into the stomach where they imbibe water to cause them to swell and also to become slippery, thus enhancing their retention in the stomach. Imbided water from the gastric fluid dissolves the drug entrapped in the particles and the resulting solution diffuses from the dispersed particles, assuring that no solid drug, which is more irritating, contacts the mucosal tissue. A number of embodiments of the dosage form utilizing different drugs are exemplified and the benefits are explained. Aspirin is one example.</p>		

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5 ALKYL-SUBSTITUTED CELLULOSE-BASED
 SUSTAINED-RELEASE ORAL DRUG DOSAGE FORMS

Cross-Reference to Related Application

 This application is a continuation-in-part of patent
 application USSN 07/858,320, filed March 5, 1992.

10 Technical Field

 This invention is in the general field of
 pharmacology and relates specifically to alkyl-substituted
 cellulose-based sustained-release drug dosage forms whose rate
15 of drug release and dissolution is not dependent upon
 crosslinking and that may be made by direct compression and
 other procedures without binders.

 BACKGROUND OF THE INVENTION

20 This invention is an improvement on the sustained-
 release oral drug dosage forms described in U.S. Patent No.
 5,007,790. Those dosage forms consist of a plurality of solid
 particles composed of a solid drug dispersed in a hydrophilic
 water-swellaable crosslinked polymer. The polymers of the
25 particle imbibe water, causing the particles to swell and the
 drug contained in the particle to dissolve and leach from the
 particle. After the drug has leached from the particles, the
 crosslinks of the polymer cleave to allow the polymer to
 dissolve.

30 In contrast to the polymers described in U.S. Patent
 No. 5,007,790, the polymers used in the present invention are
 not crosslinked. They are thus inherently safer in that
 possible toxicity from any residual crosslinking agent is
 avoided. In addition, the particles made from the present
35 polymers may be formed into solid bodies (e.g., tablets) by
 direct compression without binders. Binders had to be added
 to the polymers of the prior patent in order to compression-
 mold the particles. This lack of binder makes the dosage

forms easier to fabricate and less expensive. Finally, once the particles have been ingested and they imbibe water, they swell to a size which promotes retention, and they become exceptionally soft and slippery. As a consequence of the latter, they tend to resist expulsion from the stomach by the peristaltic motion of the stomach walls better than the particles of the prior patent.

Hydroxyalkylcelluloses have been used commercially as binders for sustained release tablets, and as ingredients in ophthalmic preparations.

SUMMARY OF THE INVENTION

The invention is a sustained-release oral drug dosage form for releasing a solution of a drug into the stomach comprising a plurality of solid particles or pellets of a solid-state drug dispersed within a non-crosslinked alkyl-substituted cellulose that (i) swells unrestricted dimensionally via imbibition of gastric fluid to increase the size of the particles to promote onset of the "fed mode" in the patient, with consequent increase in gastric retention time of the particles, and makes the particles slippery to further promote their retention within the stomach, (ii) permits dissolution of the dispersed drug by imbibed gastric fluid while the drug is within the particle and release of the resulting solution, thus assuring that only drug in solution contacts the gastric mucosa, (iii) protects undissolved drug in the particles from stomach enzymes or pH effects so that undegraded drug is delivered to the stomach or duodenum, and (iv) maintains its physical integrity over at least a substantial portion of the time period during which the drug is released into the stomach and then dissolves, wherein the dosage form is in the form of individual particles. When presented in the form of a tablet or capsule that maintains the particles in a packed mass prior to their ingestion, the tablet or capsule rapidly disintegrates in the gastric fluid to permit the particles to disperse in the stomach.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1 and 2 are graphs of the release experiments described in Example 1, *infra*.

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DESCRIPTION OF THE PREFERRED EMBODIMENT

The dosage forms of the present invention are effective for administering drugs of limited solubility in gastric fluid that are capable of acting locally within the gastrointestinal tract or systemically by absorption into circulation via the gastrointestinal mucosa. The drug should be solid and not so water-soluble that it is rapidly leached from the particles over a very short time (i.e., less than about four hours), nor so insoluble that too little is leached from the particles to achieve the desired therapy. Thus, drugs having a solubility that permits them to dissolve and leach from the particles at a rate that provides the pharmacokinetics for therapy and the desired duration of treatment are selected. Normally, the solubility of the drug (measured in water at 37°C) will be in the range of 0.001% to about 35% by weight, more normally 0.001% to 5% by weight.

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The invention is particularly useful for delivering drugs that are irritating to the gastrointestinal tract such as the mucosa of the stomach as a solid, drugs that are efficacious when administered in a sustained manner within the stomach, and drugs that are labile in the environment of the stomach. For instance, aspirin, which may be highly injurious to the gastric mucosa in its solid state, is advantageously administered in either high doses (generally 800 to 1400 mg over 10-14 hours) for analgesia or arthritis or at low doses (usually 20 to 100 mg, preferably about 30 mg) over a 4 to 14 hour period for prevention of heart attack and stroke, reduced risk of colon or rectal cancer, prevention of migraine, or prevention of pregnancy-induced hypertension. Irritation is avoided or limited because the initially solid drug is slowly released in solution and also because the drug-containing particles are dispersed, thereby limiting the concentration drug at any one site. The controlled delivery of the present

particles allows for treatment with less total amount of drug, which further reduces the irritation effect.

Drugs which are effective for eradicating *Helicobacter pylori* from the submucosal tissue of the gastrointestinal tract, particularly the stomach, to treat stomach and duodenal ulcers, treat gastritis and esophagitis, and reduce risk of gastric carcinoma may also be administered effectively via the invention because the invention provides enhanced gastric retention and prolonged release. Drugs and drug combinations suggested for this indication include bismuth salts such as bismuth subsalicylate and bismuth citrate, metronidazole, and amoxycillin, other antibiotics such as tetracycline, neomycin or erythromycin, or combinations of such drugs. Preferred drugs for this indication are a bismuth salt plus metronidazole, amoxycillin plus metronidazole, and amoxycillin or a bismuth salt plus omeprazole.

Alternatively, the invention can be used with conventional ulcer treating drugs such as an H-2 antagonist (e.g., cimetidine or ranitidine) or an antacid such as calcium carbonate. In this regard, some agents appear to be more effective in an anacidic stomach; hence the presence of such acid reducing agents may be desirable.

Drugs such as peptides and proteins which are labile to the effects of gastric pH or gastric enzymes may also be effectively administered via the invention because the undissolved portion of the drug is physically protected within the particle until its dissolution and release, allowing for continuous delivery of undegraded drug at or near the site for the most efficient absorption of many such drugs -- e.g., from the lower stomach through the duodenum to the upper part of the small intestine which is the site within the gastrointestinal tract for the most efficient absorption of many molecules which are too large for significant absorption elsewhere. The ultimate advantage of this feature is that it allows for the oral administration of some therapeutic agents which otherwise require administration by injection. Examples of such agents are calcitonin, calcitriol and insulin.

Another example is that group of drugs known as proton pump inhibitors, such as omeprazole, which benefit from the slow release to optimize absorption while being protected from gastric acid.

5 This feature also allows for enhanced opportunity for bioabsorption of therapeutic agents which, while they may be absorbed to some extent from the G.I. tract, they are not under normal circumstances efficiently absorbed. Examples of such agents are cyclosporins, acyclovir, cephalosporins, 10 interleukins, nitrofurantoin, and the ergot alkaloids.

Since it provides drug by continuous delivery instead of the pulse-entry associated with conventional dosage forms, two particularly significant benefits obtained with the present invention are: (1) The reduction in side effects from 15 the drug, and (2) The ability to effect treatment with less frequent administration of the drug(s) being used. The following drugs when formulated in accordance with the invention provide these advantages, as well as other advantages as noted: Reduction in the side effects of 20 angioedema, and agranulocytoses from angiotensin converting enzyme inhibitors such as elanopril maleate and captopril; reduction of anti-cholinergic (drying) and sedative side effects while providing long-lasting desired effects of antihistamines, such as clemastine fumarate; prolonged 25 activity through gastric retention, less frequent administration requirements, and reduced side effects such as liver dysfunction, rhabdomyolysis, rash and headache, from cholesterol lowering drugs such as lovostatin; provision of more prolonged effects of antidepressant agents such as 30 fluoxetine, with a reduction of typical side effects of these agents, such as insomnia and stomach upset; reduction in the required administration from three or four times daily to once daily, and reduction of the side effects, of antiepileptic drugs such as carbamazepine; and steady, prolonged control of 35 pain, with reduced drug toxicity, from potent analgesics such as meperidine are obtained.

Benefits by way of reduction of the level of irritation and elevated LDL cholesterol may be obtained

through use of formulations of this invention with blood platelet aggregation inhibitors such as ticlopidine.

A variety of similar benefits may be obtained with other types of drugs. Thus, provision, via controlled sustained delivery and gastric retention, of medication prolonged sufficiently to extend through the night so as to alleviate early morning hypertension, the cause of many heart attacks; and also reduction in the required frequency of administration to once daily dosing; of calcium channel blockers, such as verapamil, diltiazem, nifedipine, or nicardipine are obtained. Use of the invention provides, via gastric retention of the system, for more effective utilization of gastrointestinal prokinetic agents such as cisapride. The invention also enhances the treatment of gastroesophageal reflux disease by providing prolonged, local effects of agents that improve the competency of lower esophageal sphincter (LES) muscles. Such agents, which act directly on the LES muscles, include pentagastrin, PG-F2, and metaclopramide.

Other drugs that may be advantageously administered via the invention include, without limitation, H-2 antagonists or calcium carbonate for ulcer treatment/prevention; non-steroidal anti-inflammatory agents (NSAIDS) such as indomethacin, ibuprofen, naproxen and piroxicam; steroids such as prednisone, prednisolone and dexamethasone; other NSAIDS such as diclofenac and ketorolac; acyclovir for the treatment of viral diseases such as herpes; tamoxifen for treatment of cancer; chlorpheniramine maleate for allergic disorders; potassium chloride for potassium supplementation, and peptides or other labile molecules such as protease inhibitors for treating AIDS.

The solid drug or drugs are dispersed in the selected alkyl-substituted cellulose such as hydroxyethylcellulose or hydroxypropylcellulose which ultimately dissolve in the gastrointestinal (G.I.) tract in a predictably delayed manner. The hydrophilicity and water swellability of these polymers cause the drug-polymer particles to swell in size, become slippery, and in the

gastric cavity permit the ingress of water into the particle. The release rate of the drug(s) from the particles is primarily dependent upon the rate at which the drug(s) is leached from the particles, which in turn is related to the dissolution rate of the drug, the particle size and drug concentration in the particle. Correlatively, because these polymers dissolve very slowly in gastric fluid, the particles maintain their integrity over at least a substantial portion (i.e., at least about 90% and preferably over 100% of the intended dosing period). Thereafter the polymer will slowly dissolve. As indicated previously, such dissolution does not involve chemical degradation (i.e., cleavage of crosslinks) of the polymer and its dissolution is thus innocuous. Typically the polymer will have completely dissolved within 8 to 10 hours after the intended dosing period.

All alkyl-substituted cellulose derivatives in which the alkyl groups have 1 to 3 carbon atoms, preferably 2 carbon atoms, and having suitable properties as noted are contemplated. Cellulose is used herein to mean a linear polymer of anhydroglucose. Additional examples of suitable alkyl-substituted cellulose are: methylcellulose, hydroxymethylcellulose and carboxymethylcellulose. In general, suitable alkyl-substituted celluloses have a mean viscosity from about 1,000 to 4,000 centipoise (1% aqueous solution at 20°C). A preferred polymer is hydroxyethylcellulose available from Aqualon Company (Wilmington, Delaware) referred to as Natrasol® 250HX, NF. It has a viscosity of a 1 percent solution at 20°C of from 1500 to 2500 centipoise.

The drug/polymer mixture is in the form of a plurality of particles. The solid drug is preferably dispersed homogeneously in the polymer, although it need not be. The weight ratio of drug to polymer in the mixture or dispersion will normally be 1:4 to 2:1, preferably 1:2 to 1:1, and most preferably 2:3 to 1:1. The particles are preferably spherical in shape but may be in the shape of less regular, but equant, granules.

The swollen particles will be of a size that promotes their retention in the stomach when the patient is not in the fed mode (i.e., presence of food) and particularly when the patient is in the fed mode. This will normally be in the range of about 2 to 15 mm, preferably about 6 to about 12 mm (measured as the diameter for spherical particles or largest dimension for irregularly shaped particles), but may be larger. Since the particles will typically swell up to twice their original diameter in about 40 minutes and three times their original diameter in about 5 hours, the initial particle size is usually in the range of about 1 to 5 mm, preferably 2 to 4 mm. Because the particles retain their physical integrity during the dosing period, their swollen volume will remain substantially constant (i.e., typically less than a 25% decrease) over the dosing period.

For drugs not intended for gastric retention, a useful particle size range for the initial particles is about .5 to about 3 mm, with a preferred size of about 2 mm. Again, the swollen particles are about three times their initial diameter.

The particles may be formed into a packed mass for ingestion by conventional techniques. For instance, the particles may be encapsulated as a "hard-filled capsule" or a "soft-elastic capsule" using known encapsulating procedures and materials. The encapsulating material should be highly soluble so that the particles are rapidly dispersed in the stomach after the capsule is ingested. Alternatively and preferably, the particles may be mixed with tableting excipients compressed into a tablet or pill. Each unit dose, whether capsule or tablet, will preferably contain particles of a size which when swollen enhance the potential for gastric retention. With respect to the number of particles per unit dose, a useful quantity for addition to a size zero capsule is about 14 particles, preferably spheres of about 4 mm diameter, 37 spherical particles of about 3 mm diameter, or 115 spherical particles of about 2 mm diameter. A workable range of particles is about 10-200 spherical particles in either a capsule or a tablet. In the preferred embodiment utilizing a

tablet dosage form, the tablet contains, in addition to any inert matrix that may be utilized, from about 5-20 spherical particles of a size range from about 1 to about 4 mm in diameter.

5 With respect to the inert matrix in the dosage form, in the preferred embodiment an ionizable swelling agent is included which functions to osmotically increase the rate and extent of water imbibition that occurs when the particles are exposed to gastric fluid. A variety of pharmaceutically
10 acceptable substances which ionize are contemplated. Ionizable salts such as sodium chloride is one such material. Other inorganic salts that are pharmaceutically acceptable are potassium sulfate and magnesium sulfate. Ionizable organics, such as ionic polymers, for example, sodium
15 carboxymethylcellulose, can also be used. The salt sodium bicarbonate is another example which is particularly useful in an antacid product. The increased swelling effect provided by the swelling agent enhances the propensity of the spheres to be retained in the gastric cavity. The addition of ionized
20 salts also provides for increased rate of drug diffusion from the polymer matrix, which is a useful feature for drugs whose solubility is extremely low, and which otherwise could not be delivered from the system at a high enough rate to be useful.

As an example, it has been found that sodium
25 chloride at a concentration of 10% by weight in a matrix of 45% aspirin/45% hydroxypropyl cellulose by weight doubles the rate of swelling of spheres made from this composition, compared to spheres devoid of sodium chloride, when the spheres are suspended in an aqueous medium; and the rate of
30 aspirin delivery from such a system is approximately tripled. In the preferred embodiment, sodium chloride can be used for purposes of enhancing the swelling rate of polymeric spheres at a concentration range of from about 1% to 5% by weight, preferably at a concentration of about 1% or 2% by weight.
35 This is a generally suitable range for swelling enhancing agents but any effective amount otherwise compatible with the drug and its use is contemplated.

An alternative to the preferred embodiment for enhancing sphere swelling properties involves addition of sodium starch glycolate, used in concentration of from about 0.5% to 3%, and preferably at about a 1% concentration by weight.

As noted, in addition to an increase in the rate of sphere swelling caused by the ionizable swelling agent, the degree or extent of swelling is also increased. For example, where a 10% by weight of sodium chloride is incorporated in a particle of this invention, a 60% increase over the size of the sphere swollen without benefit of the salt inclusion is obtained.

Another additive for the inert matrix in the dosage form may be desirable when the selected drug is so soluble that it may be released at a rate more rapid than desired. Examples of such drugs are potassium chloride and various peptides used as pharmaceuticals. In order to reduce the rate of release of these high solubility drugs, the particles are formulated to include a long chain fatty acid ester of glycerin, such as glyceryl monooleate. As illustrated in the examples below, the glyceryl ester is first mixed with the selected drug and thereafter the drug/glyceryl ester combination is mixed with the cellulose polymer. In general, long chain fatty acid esters of glycerin in which the fatty acid moiety has 15 to 21 carbon atoms bonded to its carboxyl group are contemplated, with the monoester of glycerin being preferred. Both saturated and unsaturated fatty acids may be utilized in ester formation, including palmitic, stearic, oleic, linoleic and linolenic acids. In addition to glycerin monooleate, other preferred esters are glyceryl behenate and glyceryl monostearate. Suitable reduction in release rate of the drug is obtained by incorporating an effective amount of the selected glyceryl ester. In general, highly soluble drugs will exhibit the desired reduced release rate by adding about .5 to 4 moles of the glyceryl ester for each mole of drug.

The particulate drug/polymer mixture may be made by a number of mixing and comminution techniques with the final

particle being fabricated by one of the following five methods:

5 (1) Extrusion and spheronization, using for example a Luwa Corporation Extruder/Marumerizer, available from Luwa Corporation Process Division, Charlotte, North Carolina.

10 (2) Direct compression, using multicavity hemispherical punches and dies, available from Elizabeth Carbide Die Company, Inc., McKeesport, Pennsylvania. The punches and dies are fitted to a suitable rotary tableting press, such as the Elizabeth-Hata single-sided Hata Auto Press machine, with either 15, 18 or 22 stations, and available from Elizabeth Hata International, Inc., North Huntingdon, Pennsylvania.

15 (3) Injection or compression molding using suitable molds fitted to a compression unit, such as available from Cincinnati Milacron, Plastics Machinery Division, Batavia, Ohio.

20 (4) Rotogranulation, using equipment for this procedure available from Glatt Air Techniques, Inc., Ramsey, New Jersey.

25 (5) For non-spherical shapes, the method consists of the following steps: (a) compaction of the powder mix, (b) milling of the compacted mass, (c) selective sieving of the milled product, and (d) recycling the material not selected by the sieving process.

30 When direct compression is used as the manufacturing process to make spheres, the addition of lubricants may be helpful and sometimes very important to prevent "capping" of the particle when the pressure is relieved. This is increasingly important as smaller spheres or particles are made. Useful agents include magnesium stearate (in a concentration in the powder mix of from 1% to 8%, preferably about 3% by weight), and hydrogenated vegetable oil (about 1% to 5% by weight, preferably about 2% by weight). Hydrogenated vegetable oil is an NF (The National Formulary) substance
35 comprising hydrogenated and refined triglycerides of stearic and palmitic acids.

Alternatively, capping may be eliminated with lower concentrations of the lubricants or other excipients if a unit shape is chosen part way between a sphere and a right cylinder. That is, the unit is a cylinder with convex, instead of flat, ends. Thus another embodiment of the invention is a plurality of pellets, instead of spheres, which are either prolate or oblate spheroids of approximately equant dimensions. That is, the diameter of the circular cross-section is near but is not equal to the length of the axis normal to the section. As with the sphere dimensions described elsewhere, this dimension is from about 1 to about 5 mm, and preferably about 2-4 mm.

The dose of drugs from conventional medication forms is specified in terms of drug concentration and administration frequency. In sharp contrast, because it delivers a drug by continuous, controlled release, a dose of medication from the system described in the invention is specified by drug release rate, and by duration of the release. It is the continuous, controlled delivery feature of the system that allows for (a) reduced drug side effects, since only the level needed is provided to the patient, and (b) less need to provide for precision in the timing of repeated administrations.

Different drugs have different biological half-lives, which determine their required frequency of administration (once daily, four times daily, etc.). Thus, when two or more drugs are co-administered in one conventional medication unit, an unfavorable compromise is often required, resulting in an underdose of one drug and an overdose of the other. In an alternate dosage form of this invention, a plurality of drug-containing spheres are provided, some of the spheres containing a first drug/polymer composition, and designed to release its drug at its ideal rate and duration (dose), while other spheres may contain and release a second drug with the same or different polymer than used with the first drug at its ideal rate and duration which is different from the other drug. Control of the release rate of the differing drugs may also be obtained by combining different amounts of each of the drug/polymer particles in a common

dosage form such as a tablet. For example, where two drugs are combined in a tablet made from 20 particles, 5 particles may contain one drug and 15 particles would contain the other drug.

5 Examples of drug combination products based on the invention are norethindrone plus ethinyl estradiol, a combination useful for fertility control, and acetaminophen plus codeine, a potent analgesic combination. In both
10 examples, each single ingredient can be provided at its optimum release rate for optimum pharmacokinetics and biological activity.

 This feature of the invention which allows for co-administration of physically separated drugs also allows for combination products which are otherwise impossible due to
15 chemical incompatibility of the chosen drugs when formulated together.

Example 1

20 Experimental pellets were made by mixing dry hydropropylcellulose (HPC) (Klucel, H.F., Hercules) and dry aspirin (ASA) powder in varying proportions and compressing the mixture into 3 mm diameter cylinders 3 mm high. The composition of these pellets is set forth below.

25	Pellet Designations	Wt (g)	WT ASA (mg)	% HPC (Wt)
	DMS-49-A	408.9	347.6	15
30	DMS-49-B	435.4	304.8	30
	DMS-49-C	419.8	209.9	50

 Cumulative release experiments were performed using a Vankel VK 600 (Six-Spindle Paddle Dissolution Tester) with Rotating Basket Assembly (USP Method 1 with standard 40 mesh
35 baskets and standard 3/8" diameter shafts) at 50 rpm and 37.0°C. The release of ASA was monitored as a function of time in simulated gastric fluid. The amount of ASA was determined using a BECKMAN DU-65 spectrophotometer at wavelengths of 247 nm and 300 nm.

40 The release of ASA was determined at 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0 and 7.0 hour time points. The release

profiles for the formulations are reported in Figures 1 and 2. The release profile for a conventional 325 mg aspirin tablet (no HPC) is also reported.

5 The results indicated that the conventional ASA tablet released more than 90% ASA within half an hour, while the invention pellets showed steady controlled release of ASA over the period of investigation (7 hours).

10 DMS-49-A was also evaluated in gastric irritation tests on female New Zealand white rabbits. Each rabbit was anesthetized using an intramuscular injection of xylazine and ketamine, given at 5-8 mg/kg and 35-40 mg/kg, respectively. The abdomen and the cervical area was then shaved. A surgical cutdown was performed to place a catheter into the jugular vein for maintaining anesthesia throughout the entire exposure
15 period. The maintenance anesthesia was sodium pentobarbitol given at 13 mg/kg as needed. An endotracheal tube was then inserted to facilitate normal respiration.

In the anesthetized animal model a section of the colon, immediately proximal to the cecum, was isolated with
20 the mesenteric vascular system intact. Two ligatures were placed approximately 15-20 cm apart around the colon section. The isolated section was then freed from the remaining intestine by cutting between the ligatures, taking care to leave the vascular and nervous systems intact. A longitudinal
25 incision was made along the entire length of the isolated colon section and the fecal material removed. The isolated colon section is then placed onto a three-cell test chamber which forms the floor of the test cell. The test cell is continuously perfused with Lactated Ringer's solution at a
30 rate of 2.2 ml per minute using a Model 975 Harvard pump. The test chamber is allowed to equilibrate for one hour to maintain a constant temperature of 37°C ($\pm 2^\circ\text{C}$). After the 1 hour equilibration period, the test material and/or positive control material ("Ten K," a commercially available potassium
35 supplement that is highly irritating to the G.I. tract) is applied to a computer-generated, randomly selected chamber. The control chamber constituted perfusion of the Ringer's solution only. The test and positive control materials were

applied in solid form. Each test cell continues to be perfused with the Ringer's solution for the entire 6 hour exposure period.

5 A quantity of the test material was chosen such that the total milligram amount of aspirin delivered over the 6-hour exposure period was equal to the total dose of aspirin provided by the positive control.

10 After 6 hours of continuous exposure, each rabbit was euthanized using an intravenous injection of sodium pentobarbital given at approximately 100 mg/kg. The isolated section of exposed colon was removed from the intestine and evaluated for macroscopic evidence of irritation for both degree (0-4) and area (0-6.40 cm²). These two values are then multiplied to calculate the Irritation Index which reflects a combination of the severity of the response and the area affected. The results are reported in the table below.

20	<u>Test Material</u>	<u>Source</u>	<u>Area</u>	<u>Mean Irritation Index</u>
	Lactated Ringer's	0	0	0
	Aspirin	4.00	4.48	17.93
25	DMS-49A	2.94	1.61	5.07
	Ten-K	3.44	4.12	16.24

30 As indicated, the mean irritation index for the invention formulation was approximately one-third that of the conventional aspirin formulation and the positive control formulation.

Example 2

35 Aspirin tablets of the invention are manufactured according to the following four-step procedure:

(1) A combination of 40.0 Gm aspirin dry powder, 258.50 Gm dry hydroxypropylcellulose (HPC), and 1.50 Gm dry magnesium stearate is ground to 100 mesh, and mixed in a suitable blender.

40 (2) The above mixture is compressed into essentially spherical pellets of 3 mm diameter, using a rotary press fitted with 3 mm hemispherical, landed punches. Except

for minor lossage, this procedure will result in a total mass of 300 Gm, representing approximately 10,000 pellets, with an individual weight of 30 mg per pellet.

(3) A combination of 750 mg magnesium stearate, 15 Gm powdered corn starch, 80 Gm lactose and 54.25 Gm HPC, all previously dried, are blended together in a PK blender to assure even mixing of the uneven-sized ingredients, while protecting from moisture. This blend may be compressed into one-inch diameter, one-quarter inch thick tablets, using a rotary tablet press fitted with punches and dies suitable for this size, and the tablets produced by this precompression ("slugging") procedure are milled in a suitable mill, and sized by sieving to produce a fraction of irregular surfaced, essentially equant granules of approximately 3 mm in cross section. Granules too fine or too course are recycled through the precompression, milling and sieving process in order to reduce waste.

(4) A combination of 300 Gm of pellets produced by step (2) and 150 Gm of granules produced by step (3) are directly compressed into 1.1 cm diameter, 4.0 mm thick tablets with slightly convex faces, using a rotary press and a tablet punch with slightly convex faces and a die volume set to accept 450 mg of this mixture.

Tablets so produced disintegrate within 20 minutes in the stomach following ingestion, with the release and dispersion of ten spherical pellets, which swell to a diameter of 10 mm within 30 minutes, facilitating gastric retention. The pellets collectively release 40 mg of aspirin into the gastrointestinal tract over a period of from 8 to 10 hours. During this time the aspirin is released in the solution state rather than the solid state. Moreover, the pellets disperse within the stomach. Both dispersion and solution-state delivery operate to reduce the G.I. irritation from the delivered aspirin.

Example 3

Aspirin capsules of the invention are prepared by the same procedure outlined in Example 2, except that:

The quantities of ingredients used in step (1) are 11.11 Gm aspirin dry powder, 287.39 Gm dry hydroxypropylcellulose, and 1.5 Gm dry magnesium stearate.

5 Step (4) of Example 2 is replaced by the following procedure: 300 Gm of pellets produced by step (2) of Example 2 are utilized as feed for a capsule filling operation in which 36 spheres of 3 mm diameter size are filled into each size zero gelatin capsule.

10 These capsules, following ingestion, rapidly disintegrate with the dispersion of the spheres, which release a total of 40 mg over a period of from 8 to 10 hours.

Example 4

15 Example 2 is repeated except that the 40.00 Gm of drug (aspirin) is replaced by 200 Gm of bismuth subcitrate or of bismuth subsalicylate.

Example 5

20 The following ingredients are dried, ground and blended together in a "twin shell" blender for 210 minutes: 111.11 Gm metronidazole, 111.11 Gm bismuth subcitrate, 1.5 Gm magnesium stearate, and 76.28 Gm hydroxyethylcellulose. This mixture is compressed into spherical pellets 3 mm in diameter, using a rotary press fitted with 3 mm hemispherical dies.

25 This procedure produces approximately 300 Gm of pellets, each weighing 30 mg (approximately 10,000 pellets). These pellets are filled into size zero gelatin capsules, with the result that each capsule will contain 36 pellets. Upon ingestion, such capsules disintegrate rapidly in the G.I. tract, allowing

30 dispersal of the pellets, which then swell to facilitate gastric retention, and collectively deliver 400 mg of both metronidazole and bismuth subcitrate over a period of from 8 to 10 hours to eradicate ulcer-producing local organisms.

35

Example 6

Example 5 is repeated except that the 111.11 Gm of bismuth subcitrate is replaced with a like amount of amoxycillin.

Example 7

Example 4 is repeated except that the initial ingredients and their amounts are replaced with: 138.89 Gm amoxycillin, 55.55 Gm ranitidine, 1.50 Gm magnesium stearate, and 104.06 Gm hydroxypropylcellulose. The final dosage form thus fabricated will deliver 500 mg of amoxicillin and 200 mg of ranitidine over a time period of from 8 to 10 hours.

Example 8

Example 7 is repeated except that ranitidine is replaced by a like amount of cimetidine.

Example 9

Example 7 is repeated except that ranitidine is replaced by a like amount of omeprazole.

Example 10

The procedure of Example 2 is repeated except that step (2) of the example is replaced with the following. The powder mixture from step (1) is granulated using minimal amounts of glycerine/water and processed into 3 mm diameter spheres by mechanical extrusion and spheronization. To accomplish this, the flexible mass is extruded from a Luwa Xtruda Extruder (Luwa Corporation Process Division), which produces a 3 mm diameter, continuous, cylindrical extrudate; this extrudate is then broken into cylindrical pellets of 1:1 length-to-diameter ration; and these pellets are then worked into spheres of 3 mm diameter by action of a Nica spheronizer and dried.

Example 11

Step (3) of Example 2 is repeated in which 750 mg of magnesium stearate is replaced by 600 mg of hydrogenated vegetable oil.

Example 12

Example 2 is repeated in which the ingredients of step (1) are replaced by 40 Gm aspirin, 15 Gm sodium chloride, 243.5 Gm hydroxyethylcellulose, and 1.5 Gm magnesium stearate.

Example 13

Example 12 is repeated in which 15 Gm of sodium chloride are replaced by a like amount of potassium sulfate.

Example 14

Example 2 is repeated in which the rotary press of step (2) is fitted with concave punches and cylindrical cavities to produce either prolate or oblate spheroid shapes of resulting compressions, whose circular cross sections measure from 3 to 5 mm, and whose heights measure from 3 to 5 mm.

Example 15

Example 2 is repeated in which the process of compression by rotary press in step (2) is replaced by the process of pellet formation by injection or compression molding, using molds fitted to a suitable compression unit (Cincinnati Malacron, Batavia, Ohio).

Example 16

Example 2 is repeated in which the process of compression by rotary press in step (2) is replaced by the process of pellet formation by use of a rotogranulator (Glatt Air Techniques, Ramsey, New Jersey).

Example 17

Example 2 is repeated in which step (2) is replaced with the following: The mixture of step (1) is compacted by use of a roller compactor, and the compacted mass is then milled in a suitable mill to reduce the particle size of the material. This material is then sieved to selectively segregate and store all particles which fall within the size range of from 2 to 5 mm. The material above or below this

size range is then recycled beginning with the compaction stage.

Example 18

5 Example 2 is repeated in which
hydroxypropylcellulose is replaced by hydroxypropyl
methylcellulose.

Example 19

10 Example 2 is repeated in which
hydroxypropylcellulose is replaced by carboxymethylcellulose.

Example 20

15 Example 2 is repeated in which
hydroxypropylcellulose is replaced by hydroxyethylcellulose.

Example 21

20 Example 2 is repeated in which the mixture of step
(1) is replaced by a mixture of 150 Gm of meperidine base and
150 Gm of hydroxypropyl methylcellulose, and step (2) is
replaced by the extrusion/spheronization procedure of
Example 1.

Example 22

25 Example 21 is repeated in which the mixture of step
(1) is replaced by a mixture of 100 Gm of carbamazepine USP
and 200 Gm of hydroxyethylcellulose.

30 The final tablets produced allow for sustained
anticonvulsive effects from once or twice daily
administration, compared to three or four times daily
administration required by conventional tablets, and also
provide for reduced intensity of this drug's side effects of
cardiovascular disorder, aplastic anemia, and erythematous
rash.

Example 23

Example 21 is repeated in which the mixture of step (1) is replaced by a mixture of 40 Gm of fluoxetine base and 260 Gm of hydroxyethylcellulose.

The final tablets produced allow for sustained antidepressant effects from once daily administration, compared to twice daily administration of conventional tablets, and also provide for reduced intensity of this drug's side effects of insomnia and upset stomach.

Example 24

Example 21 is repeated in which the mixture of step (1) is replaced by a mixture of 40 Gm of lovostatin and 260 Gm of hydroxyethylcellulose.

The final tablets produced allow for sustained cholesterol-lowering effects of this drug from once daily administration, with reduced intensity of its gastrointestinal, musculoskeletal, and CNS side effects.

Example 25

Example 21 is repeated in which the mixture of step (1) is replaced by a mixture of 20 Gm of omeprazole and 280 Gm of hydroxyethylcellulose.

The dosage form of the invention protects the reservoir of undelivered drug from acid degradation of omeprazole, which is an acid-labile drug.

Example 26

Example 21 is repeated in which the mixture of step (1) is replaced by a mixture of 60 Gm of diltiazem and 240 Gm of hydroxyethylcellulose.

The final tablets produced disintegrate upon ingestion, releasing the spheres contained therein, which disperse and swell in the stomach, thus facilitating gastric retention of the system. Sustained effect of this cardiovascular drug through the night from once-daily, bedtime administration is also provided. Accordingly, patients are

protected from early morning hypertension, the cause of many heart attacks.

Example 27

5 Example 26 is repeated in which the mixture of step (1) is replaced by a mixture of 40 Gm of cisapride and 260 Gm of hydroxyethylcellulose.

10 The final tablets produced disintegrate upon ingestion, releasing the spheres containing therein, which disperse and swell in the stomach, thus facilitating gastric retention and sustained local effect of the drug. Sustained, local delivery of this prokinetic agent allows for more efficient treatment of esophageal reflux disease.

15 Example 28

 Example 21 is repeated in which the mixture of step (1) is replaced by a mixture of 500 mg calcitonin, 280 Gm of hydroxyethylcellulose, and 41.33 mg of glyceryl monooleate. In preparing the formulation, the calcitonin and the glyceryl monooleate are first mixed intimately, and this mixture is then added to and mixed with the hydroxyethylcellulose.

20 The final tablets produced disintegrate upon ingestion, releasing the spheres contained therein, which disperse and swell in the stomach, thus facilitating gastric retention of the system. Controlled delivery of this soluble drug is facilitated by the presence of glyceryl monooleate.

25 The delivery system of the invention protects calcitonin, a labile agent, from degradation effects of gastric acid and gastric enzymes while the system is retained in the stomach. Moreover, delivery of the agent is continuously provided from the system retained in the lower part of the stomach, through the duodenum, to the upper part of the small intestine, which is the most efficient site of absorption of molecules too large to be appreciably absorbed elsewhere. When delivered by this system, a sufficient amount of calcitonin, a large peptide hormone, is absorbed to be clinically useful from oral administration. Otherwise, this agent must be administered by injection.

Example 29

Example 21 is repeated in which the mixture of step (1) is replaced by a mixture of 100 Gm of cyclosporin USP, an immunosuppressive agent, and 200 Gm of hydroxyethylcellulose.

5 The final tablets produced disintegrate upon ingestion, releasing the spheres contained therein, which disperse and swell in the stomach, thus facilitating gastric retention and, through extended time of tissue exposure, increasing the amount of absorption of this otherwise
10 difficult-to-absorb drug. Further, by providing cyclosporin through low level, continuous delivery, the adverse effects of hepatotoxicity, nephrotoxicity, and hypertension are reduced.

Example 30

15 Example 10 is repeated in which the granulation from step (1) is processed into 2 mm spheres, a size sufficiently small that after swelling in the gastric fluids after ingestion they are not retained in the gastric cavity, but large enough that (a) a useful duration of controlled delivery
20 is provided, and (b) sufficient protection of the unused drug in the system is provided to be useful. The dosage form with smaller spheres is useful for the administration of drugs which do not require gastric retention.

Example 31

25 Sustained release antacid tablets of the invention utilizing calcium carbonate as the active ingredient are prepared as follows:

30 (1) A combination of 150 Gm of dry calcium carbonate, 130 Gm of hydroxyethylcellulose, and 2 Gm of magnesium stearate are ground to 100 mesh and mixed in a suitable blender.

35 (2) The mixture from step (1) is compressed into essentially spherical pellets of 4 mm diameter, using a rotary tablet press fitted with hemispherical-cavity, landed punches and dies. Except for minor losses, this procedure will produce about 282 Gm of total pellet mass, representing about 1200 pellets, each weighing about 235 mg.

(3) The pellets of step (2) are used as a feed for a gelatin capsule filling operation in which 12 pellets are filled into each size zero capsule.

5 These capsules, following oral administration, rapidly disintegrate with dispersion of the pellets, which rapidly swell to promote their retention in the gastric cavity, and collectively release therein a total of 1.5 Gm of calcium carbonate over a 6 to 8 hour time period. This sustained release of the antacid agent into the stomach allows
10 for patients who suffer from nocturnal gastric hyperacidity and/or esophageal reflux disease to sleep through the night from a single bedtime medication of a locally active agent (i.e., no systemic side effects). Less attractive alternatives for such patients are either multiple
15 administrations of a conventional medication during the night, a regimen which interrupts sleep, or the use of longer-acting agents for gastric acid reduction such as cimetidine or ranitidine, which act systemically and therefore have adverse side effects.

WHAT IS CLAIMED IS:

1. A sustained release oral drug dosage form for releasing a solution of a drug into the stomach comprising a plurality of solid particles of a solid-state drug dispersed within a non-crosslinked alkyl-substituted cellulose that (i) swells unrestrained dimensionally via imbibition of water from gastric fluid to increase the size of the particles to promote maintenance of the fed mode in the stomach and thus increase their retention within the stomach, and make the particles slippery, which also promotes their retention within the stomach, (ii) permits dissolution of the dispersed drug by imbibed gastric fluid while the drug is within the particle and release of the resulting solution, thus assuring that only drug in solution contacts the gastric mucosa, (iii) protects undissolved drug in the particles from stomach enzymes or pH effects so that undegraded drug is delivered to the stomach and duodenum, and (iv) maintains its physical integrity over at least a substantial portion of the time period during which the drug is released into the stomach and then dissolves.

2. The dosage form in accordance with claim 1 wherein the dosage form is in the form of a tablet or capsule that maintains the particles in a packed mass prior to their ingestion and then rapidly disintegrates in the gastric fluid to permit the particles to disperse in the stomach.

3. The dosage form in accordance with claim 1 wherein the cellulose is hydroxyethylcellulose.

4. The dosage form in accordance with claim 1 wherein the drug is aspirin, the sustained drug delivery time period is about 10-14 hours and the total dose of aspirin delivered is 800 to 1400 mg.

5. The dosage form in accordance with claim 1 wherein the drug is aspirin; the sustained time period is 4 to 14 hours and the dose of aspirin is 20 to 100 mg.

5 6. The dosage form in accordance with claim 1 wherein the drug is a *Helicobacter pylori* eradicator.

10 7. The dosage form in accordance with claim 6 wherein the eradicator is a bismuth salt, metronidazole, amoxycillin, or a combination thereof.

15 8. The dosage form in accordance with claim 6 wherein the eradicator is amoxycillin or a bismuth salt plus omeprazole, an H-2 antagonist, or an antacid.

9. The dosage form in accordance with claim 1 wherein the solid particles are about 1-5 mm in diameter in maximum dimension.

20 10. The dosage form in accordance with claim 1 wherein the solid particles are about 2-4 mm in diameter in maximum dimension.

25 11. The dosage form in accordance with claim 2 wherein the dosage form is a tablet, the particles are spherical and about 1-5 mm in diameter, and number about 5-20 in one tablet.

30 12. The dosage form in accordance with claim 2 wherein the dosage form is a capsule, the particles are spherical and about 1-5 mm in diameter, and number about 10-200 in one capsule.

35 13. The dosage form in accordance with claim 11 wherein the dosage form is a tablet, the particles are spherical and about 2-4 mm in diameter.

14. The dosage form in accordance with claim 12 wherein the dosage form is a tablet, the particles are spherical and about 2-4 mm in diameter.

5 15. The dosage form in accordance with claim 1 and including sufficient ionizable swelling agent to osmotically cause imbibition of water and thereby increase the rate and extent of swelling in water.

10 16. The dosage form in accordance with claim 15 wherein the swelling agent is sodium chloride and is present in the particles at a concentration of about 1 to 5 percent by weight.

15 17. The dosage form in accordance with claim 2 wherein the particles in said tablet or capsule contain a first drug and wherein said tablet or capsule also includes particles containing a second drug which differs from said first drug dispersed within a non-crosslinked alkyl-
20 substituted cellulose.

18. The dosage form in accordance with claim 17 wherein the number of said first drug particles differs from the number of said second drug particles, said numbers of
25 particles being selected to provide the desired delivered dose of each of said first and second drugs.

19. The dosage form in accordance with claim 17 wherein said first drug particles contain a first cellulose
30 polymer and said second drug particles contain a second cellulose polymer different from said first drug polymer, said polymers being selected to provide the desired release rates of said first and second drugs.

35 20. The dosage form in accordance with claim 1 wherein said drug has a release rate greater than desired because of its water solubility and including sufficient long

chain fatty acid ester of glycerin to reduce the release rate of said drug to a lower rate.

5 21. The dosage form in accordance with claim 20 wherein the drug is potassium chloride.

 22. The dosage form in accordance with claim 20 wherein the drug is a peptide.

10 23. The dosage form in accordance with claim 20 wherein the glyceryl ester is selected from glyceryl monooleate, glyceryl behenate and glyceryl monostearate, the selected ester/drug ratio being about .5 to 4 moles of ester per mole of drug.

15 24. The dosage form in accordance with claim 1 wherein said drug is cisapride.

20 25. The dosage form in accordance with claim 1 wherein said drug is calcium carbonate.

 26. The dosage form in accordance with claim 1 wherein said drug is bismuth subsalicylate.

25 27. The dosage form in accordance with claim 1 wherein said drug is Naproxen.

30 28. A method for delivering an acid-labile drug through the gastrointestinal tract comprising providing a dosage form in accordance with claim 1 wherein the unprotected solid state drug is sufficiently enzyme- or acid-labile in the gastrointestinal tract as to require administration by injection, and introducing said dosage form to a patient orally.

35 29. A method for reducing side effects of a drug and frequency of administration comprising providing a dosage

... form in accordance with claim 1, and introducing said dosage form to a patient orally..

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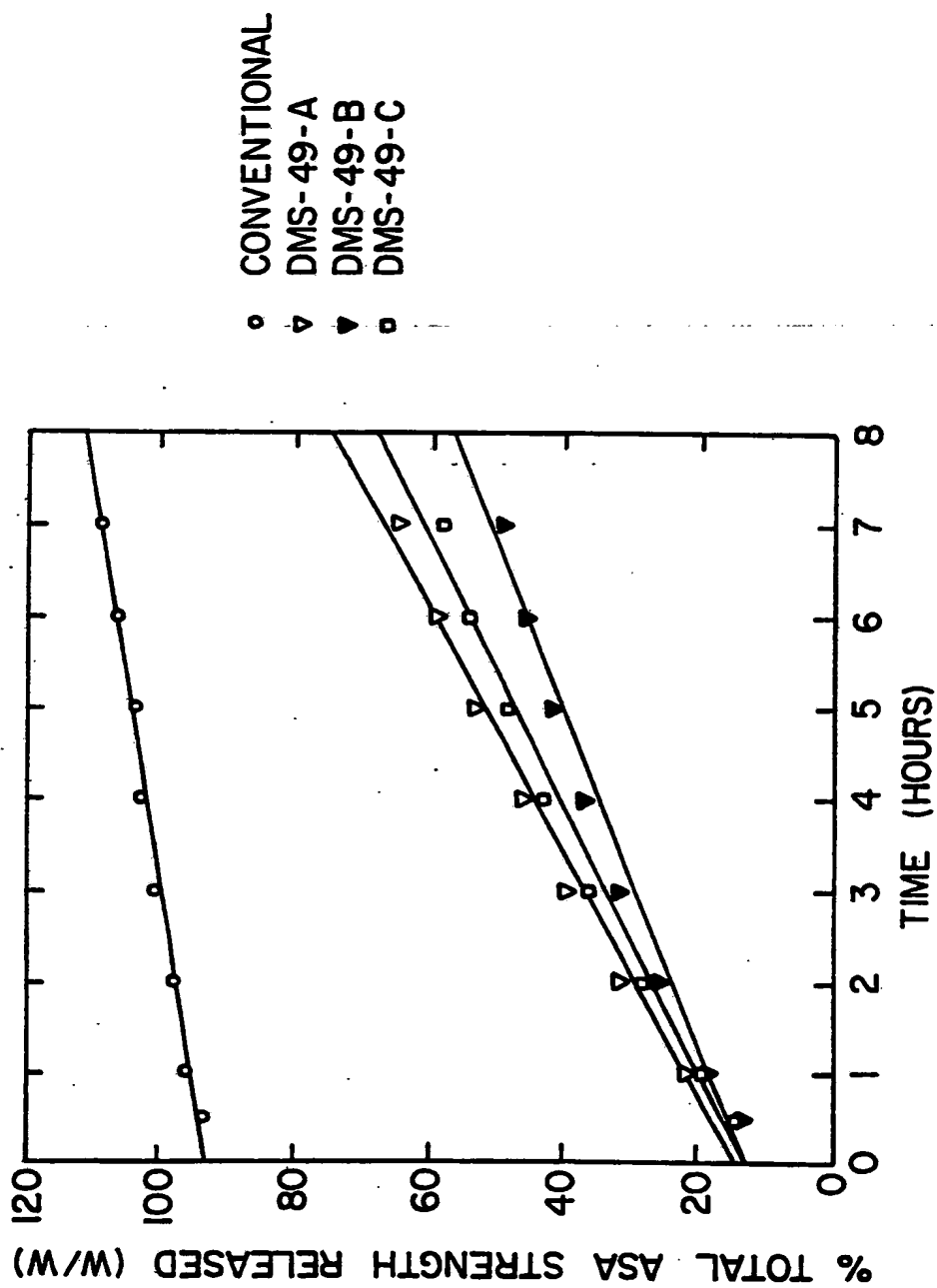


FIG. 1.

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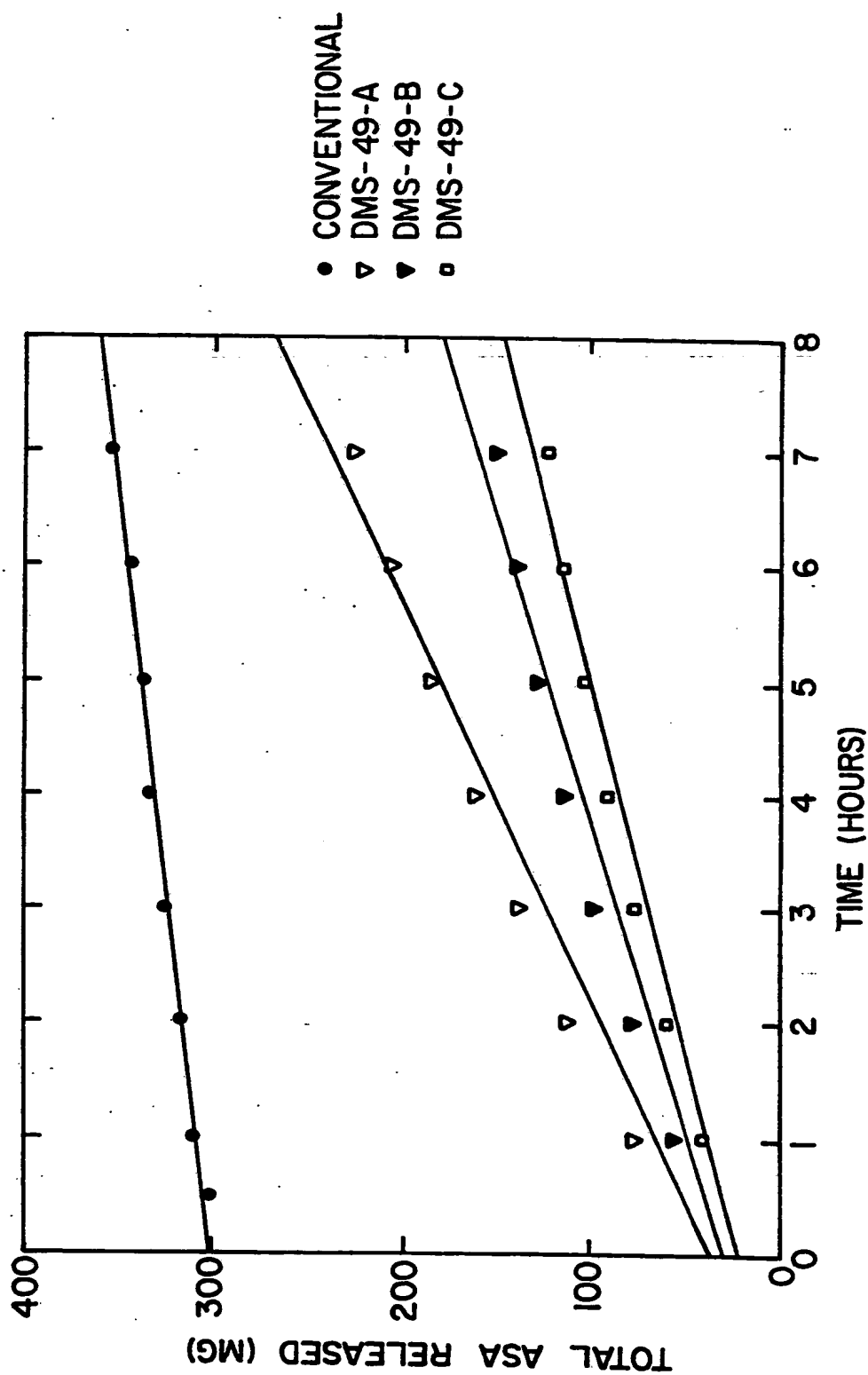


FIG. 2.

SUBSTITUTE SHEET

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 93/02420

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K9/16

II. FIELDS SEARCHEDMinimum Documentation Searched⁷

Classification System

Classification Symbols

Int.Cl. 5

A61K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸**III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹**

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	FR,A,2 304 354 (F. HOFFMANN-LA ROCHE & CIE.) 15 October 1976	1-3, 6, 8, 17-20, 23, 25, 28, 29
Y	see claims 1-4, 7, 12, 19-22, 25, 26, 30 see page 6, line 1 - line 14 see page 7, line 2 - line 15 see page 8, line 6 - line 9 see page 9, line 13 - line 17 see page 9, line 31 - line 33 see page 11, line 24 - line 31 see page 25; example 8 --- -/--	4, 5, 11, 13, 21, 27

¹⁰ Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

¹¹ later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention¹² document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step¹³ document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.¹⁴ document member of the same patent family**IV. CERTIFICATION**

Date of the Actual Completion of the International Search

18 JUNE 1993

Date of Mailing of this International Search Report

01.07.93

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

VENTURA AMAT A.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category*	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	<p>WO,A,9 204 013 (EURAND INTERNATIONAL SPA) 19 March 1992</p> <p>see claims 1,3,6 see page 6, line 12 - page 7, line 5 see page 7, line 21 - line 25 see page 8; example 1 see page 11; example 3</p> <p>---</p>	1,2,9, 10,12, 14,20,23
Y	<p>WO,A,9 011 757 (DEPOMED SYSTEMS INC.) 18 October 1990 cited in the application see claims 1,2,5,6,8 see page 3, line 26 - page 4, line 1 see page 4, line 32 - line 35 see page 5, line 17 - line 36</p> <p>---</p>	4,5,11, 13,21,27
A	<p>DE,U,9 107 805 (SOPAR S.A. DIVISION PHARMA.) 5 September 1991 see claims 1,10 see page 3 -paragraph 3</p> <p>---</p>	15,16
A	<p>FR,A,2 417 982 (NOVEX TALALMANYFEJLESZTO ES ERTEKESITO KULKERESKEDELMI RT.) 21 September 1979 see claims 1,7</p> <p>-----</p>	7,26

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claim 28-29 are directed to a method of treatment of the human body the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9302420
SA 71692

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

18/06/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A-2304354	15-10-76	AT-B- 353415	12-11-79
		AU-B- 505355	15-11-79
		AU-A- 1204976	22-09-77
		BE-A- 839604	16-09-76
		CA-A- 1073358	11-03-80
		CH-A- 630257	15-06-82
		DE-A,C 2611041	14-10-76
		GB-A- 1546448	23-05-79
		JP-C- 1465729	10-11-88
		JP-A- 51115910	13-10-76
		JP-B- 63008084	19-02-88
		JP-C- 1636785	31-01-92
		JP-B- 3000363	07-01-91
		JP-A- 63099007	30-04-88
		LU-A- 74558	27-09-77
		NL-A- 7602776	21-09-76
		SE-B- 433804	18-06-84
		SE-A- 7603325	18-09-76
		US-A- 4140755	20-02-79
		US-A- 4167558	11-09-79
WO-A-9204013	19-03-92	AU-A- 8395691	30-03-92
WO-A-9011757	18-10-90	US-A- 5007790	16-04-91
		AU-A- 5523490	05-11-90
		CA-A- 2014451	11-10-90
		EP-A- 0467975	29-01-92
		JP-T- 4507088	10-12-92
DE-U-9107805	05-09-91	BE-A- 1004757	16-01-93
FR-A-2417982	21-09-79	CA-A- 1113393	01-12-81
		CH-A- 639845	15-12-83
		DE-A- 2907215	06-09-79
		JP-A- 54135219	20-10-79
		US-A- 4199560	22-04-80

LEDIGLICH ZUR INFORMATION

Codes zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

AT	Österreich	GA	Gabon	MR	Mauretanien
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